CRYSTAL STRUCTURES OF SOME ORGANIC COMPOUNDS

A synopsis of the thesis submitted to the

Madurai Kamaraj University

For the award of the degree of

DOCTOR OF PHILOSOPHY

By

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SYNOPSIS

This thesis entitled "*Crystal structures of some organic compounds*" is based on the research work carried out by the author at the Department of Physics, School of Physics, Madurai Kamaraj University, under the supervision of PROF.S.NATARAJAN during the period 2004-2007.

The thesis contains the crystallographic studies on two distinct groups of compounds and hence is divided into two parts consisting of seven chapters. The first part deals with the crystal structure determination of compounds of piperidine/pyridine. The second part deals with the crystal structures of the complexes of some amino acids with trifluoroacetic acid and benzoic acid. For the elucidation of the structures of these molecules at atomic resolution, single crystal X-ray diffraction techniques were employed.

In **Chapter 1** of the thesis, the importance and the interest in the choice of the two distinct classes of compounds viz., substituted piperidine/pyridine compounds in **Part I** and amino acid complexes in **Part II** is dealt with.

Part I

Crystal structures of substituted piperidine/pyridine compounds

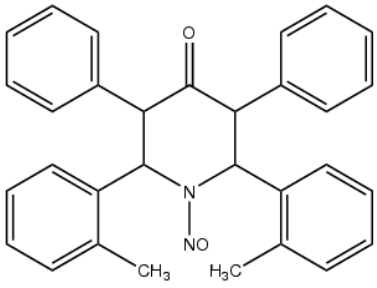
In recent years, piperidone derivatives have attracted wide attention owing to their interesting stereochemistry, intramolecular interactions involved and also for their useful biological properties. With a view to having a better understanding of weak molecular interactions and gaining some experience on the elucidation and analysis of organic molecules, it was decided to carry out the present investigations on piperidone/pyridine derivatives.

Among six-membered nitrogen heterocycles, piperidine and pyridines are important synthons for the preparation of alkaloids and medicinal agents. Piperidone derivatives act as potential inhibitors of human placental aromatase *in vitro,* and piperidin-4-ones behave as cytotoxic and anticancer agents. Many saturated and unsaturated piperidin-2-ones have been used as chiral intermediates for the preparation of numerous natural and synthetic compounds with significant anticancer, anti-HIV and glycosidase inhibition activities. On the other hand, pyridines assume much importance in organic synthesis because of the occurrence of their saturated and partially saturated derivatives in biologically active compounds and natural products such as NAD nucleotides, pyridoxol (vitamin B6), and pyridine alkaloids. Substituted pyridines have also found a number of applications such as anticorrosion agents, insecticides and as potential drug substances.

X-ray diffraction, as a tool, has become indispensable to crystal chemistry as it helps not only in solving the ambiguity in molecular structure but also helps in understanding the magnitudes and directional characteristics of different types of intermolecular interactions over the conformation and packing modes in addition to the chemists' interest to deduce their configuration. For instance, the concept C–H…

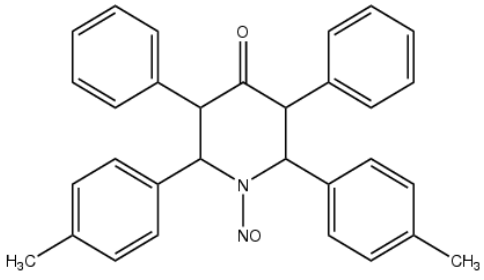
O hydrogen bond is becoming increasingly relevant and important amidst non-bonded electrostatic interactions in the design of crystal structures, leading to further investigations into the geometries and strengths of other weak intermolecular interactions including those involving π-systems. Thus, accurate results of molecular structures elucidated are invaluable experimental facts. A detailed X-ray crystallographic analysis of the above mentioned structural features of a class of compounds helps to confirm and refine previous knowledge about the nature and role of intermolecular interactions and can prove to be useful in designing molecules.

In **Part I (Chapters 2 to 5)** of this thesis, the X-ray crystal structures of a few substituted piperidine and pyridine compounds are reported. The crystal data along with the R-factors of the crystal structures of the compounds are given in Table 1. The crystal structures reported are :



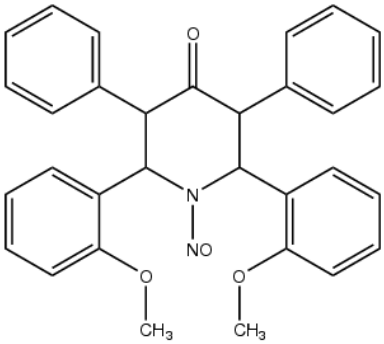
1. 2,6bis(2-methylphenyl)–1- nitroso-3,5-diphenylpiperidine– 4-one.

$[C_{31}H_{28}N_2O_2]$ **(Compound 1)**



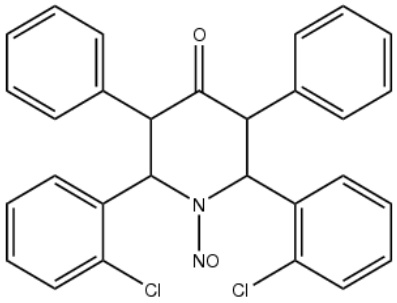
2. 2,6 bis(4-methylphenyl)–1-nitroso-3,5-diphenylpiperidine–4–one.

$[C_{31}H_{28}N_2O_2]$ **(Compound 2)**



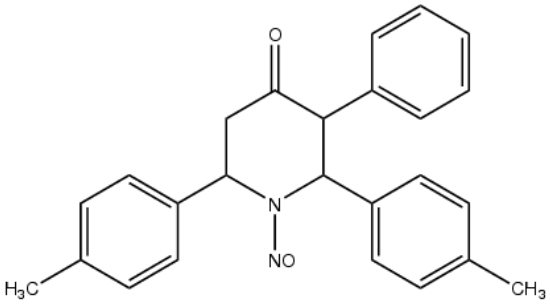
3. 2,6 bis (2-methoxyphenyl)–1- nitroso-3,5-diphenylpiperidine–4-one.

$[C_{31}H_{28}N_2O_4]$ **(Compound 3)**



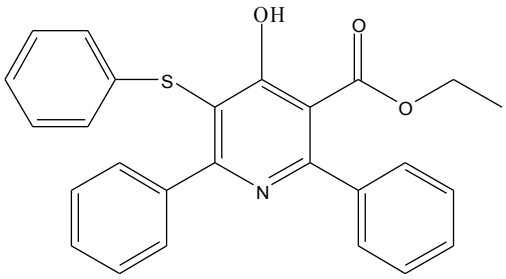
4. 2,6 bis (2-chlorophenyl)–1-nitroso-3,5- diphenylpiperidine–4-one.

$[C_{31}H_{28}Cl_2N_2O_2]$ **(Compound 4)**



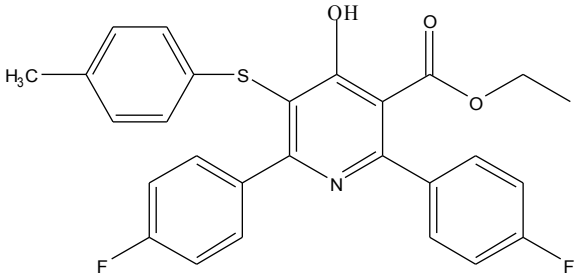
5. 2,6-bis(4-methylphenyl)-1-nitroso-3-phenyltetrahydro-4(1H)-piperidin-4-one.

$[C_{25}H_{24}N_2O_2]$ **(Compound 5)**



6. Ethyl 4-hydroxy-2,6-diphenyl-5-(phenylsulfanyl)pyridine-3-carboxylate.

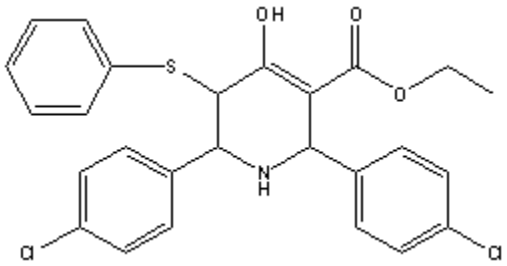
$[C_{26}H_{21}NO_3S]$ **(Compound 6)**



7. Ethyl 2,6-bis(4-fluorophenyl)-4-hydroxy-5-((4-methylphenylsulfanyl)

pyridine-3-carboxylate.

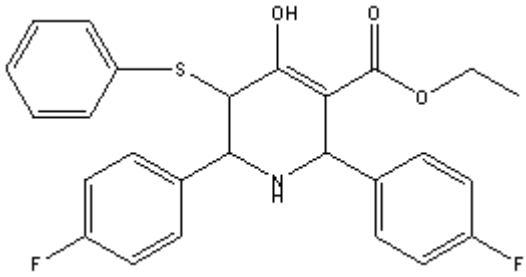
$[C_{27}H_{21}F_2NO_3S]$ **(Compound 7)**



8. Ethyl 2,6-bis-(4-chlorophenyl)-4-hydroxy-5-phenyl-1,2,5,6-

tetrahydropyridine-3-carboxylate.

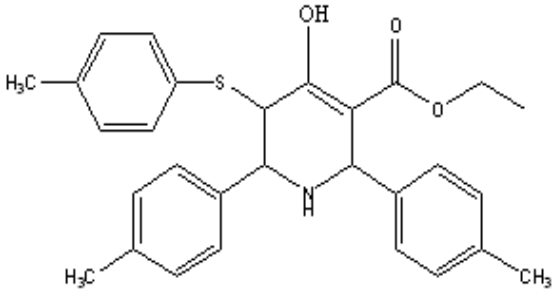
[$C_{26}H_{23}Cl_2NO_3S$] **(Compound 8)**



9. (2RS,5SR,6SR) Ethyl 2,6-bis-(4-fluorophenyl)-4-hydroxy-5-phenyl-1,2,5,6-

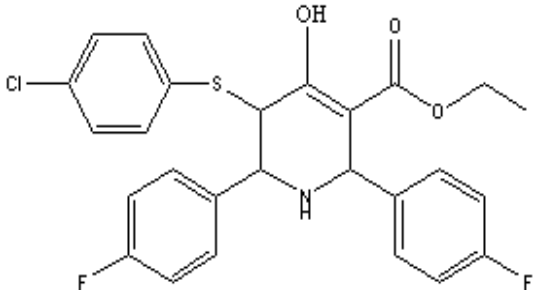
tetrahydropyridine-3-carboxylate.

[$C_{26}H_{23}F_2NO_3S$] **(Compound 9)**



10. (2RS,5RS,6RS)Ethyl 4-hydroxy-2,5,6-tri-p-tolyl-1,2,5,6-tetrahydro pyridine-3-carboxylate.

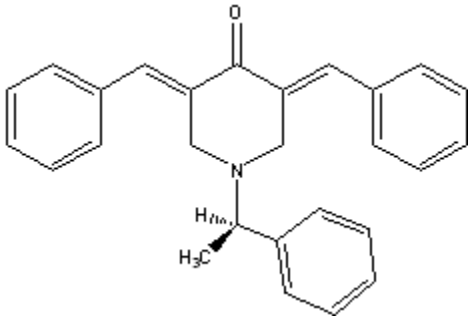
[$C_{29}H_{31}NO_3S$] **(Compound 10)**



11. (2SR,5SR,6SR)-Ethyl 5-(4-chlorophenylthio)-2,6-bis(4-fluorophenyl)-

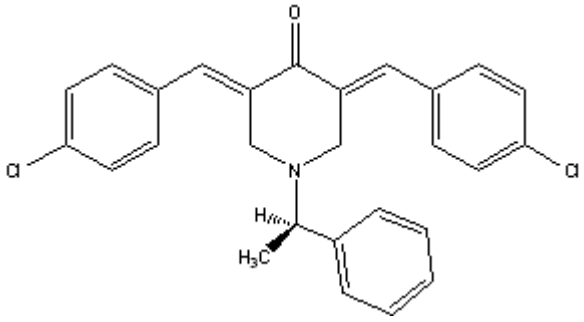
4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate.

[$C_{26}H_{22}ClF_2NO_3S$] **(Compound 11)**



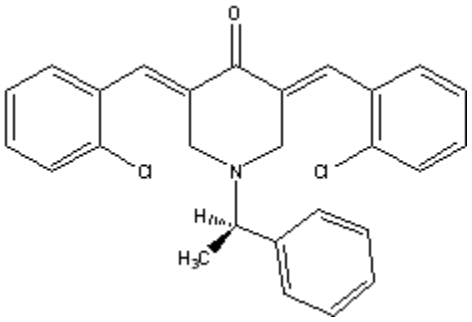
12. (R)-(1-phenylethyl)-3,5-bis[(E)-phenylmethylidene]tetrahydro-4(1H)-pyridinone.

$[C_{27}H_{25}NO]$ **(Compound 12)**



13. 3,5-bis[(E)-(4-chlorophenyl)methylidene]-1-[(R)-1-phenylethyl] tetrahydro-4(1H)-pyridinone.

$[C_{27}H_{23}Cl_2NO]$ **(Compound 13)**



14. 3,5-bis[(E)-(2-chlorophenyl)methylidene]-1-[(R)-1-phenylethyl] tetrahydro-4(1H)-pyridinone.

$[C_{27}H_{23}Cl_2NO]$ (**Compound 14)**

Chapter 2 describes the structural details of compounds 1 to 5. Compounds 1, 3 and 4 have crystallized in the monoclinic space groups with the presence of glide planes in addition to inversion centres. Compounds 2 and 5 have crystallized in the triclinic space group with the presence of inversion centre. In all the five compounds reported in this chapter, the piperidinone ring adopts a twist-boat conformation. In the case of tetra substituted piperidone derivatives, which of the two from the four prefer axial/ equatorial orientations, are decided by the steric interactions. In the case of compound 2, during the refinement of the structure, electron density peaks were located, close to inversion centers that were believed to be highly disordered solvent molecules, possibly ethyl acetate and/or diethyl ether. Attempts to model the solvent molecules were not successful. In the final cycles of refinement, this contribution to the electron density was removed from the observed data. Except in compound 2, the molecular packing in the remaining structures are due to C—H...O bonding in addition to C—H…π interactions.

Chapter 3 describes the structural details of compounds 6 and 7 . Compounds 6 and 7 have crystallized in the monoclinic space groups. In the compounds 6 and 7, the pyridine heterocycles are planar as observed in the other substituted pyridine structures. None of the substituted group forming a plane is either coplanar or orthogonal to the pyridine ring. In both the compounds (6 and 7), in the pyridine rings, the endocyclic angles are expanded or contracted due to the bulky substituents, and the strain is taken up by angular distortion rather than by bond-length distortions. C—H…O and C—H…F hydrogen bonds play prominent roles in stabilizing the

crystal structure of compound 6 and 7, respectively. The supramolecular aggregation is completed by the presence of weak C—H... π interactions.

Chapter 4 describes the structural details of compounds 8, 9, 10 and 11. All the four compounds have crystallized in the monoclinic space groups. The tetrahydro pyridine ring adopts half-chair conformation in compounds 8 and 11 and twisted half-chair conformation in compounds 9 and 10 as evident from the puckering parameters. From the values of the torsion angles it is observed that greater strain prevails in compounds 10 and 11, due to substitution in the phenylsulfanyl group. The asymmetric units of compounds 8, 9, 10 and 11 contain chiral carbon atoms and the compounds 8 to 11 are in centrosymmetric space groups and there will be by symmetry equal numbers of any enantiomers. C—H…O and some other specific interaction patterns are found in stabilizing the crystal structure of compounds 8 to 11.

Chapter 5 describes the structural details of compounds 12, 13 and 14. Compound 12 has crystallized in the orthorhombic space group and compounds 13 and 14 in the monoclinic space groups. The piperidone rings in 12, 13 and 14 adopt sofa conformation, is evident from the asymmetric parameters calculated for piperidone ring. Both olefinic double bonds have an E configuration and the aryl rings are non-coplanar with the adjacent olefinic double bonds and the planar portion of the piperidone ring in compounds 12, 13 and 14. Certain bond angles are smaller in compound 14 than in compound 13. These data imply that the aryl rings are closer to the central alicyclic ring in compound14 than in 13, which may be a contributing factor in the variation of potencies of these compounds.

Part II

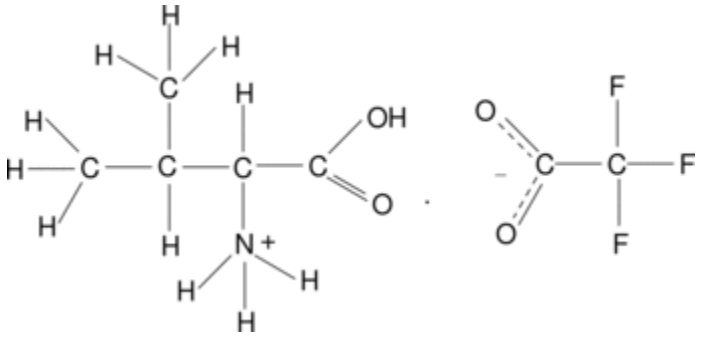
Crystal structures of amino acid-carboxylic acid complexes

Amino acids are the building blocks of proteins and an important class of molecules, which are found to exhibit specific characteristic aggregation patterns in their crystal structures. Especially, the head-to-tail hydrogen bonding patterns that have been observed in the crystal structures of amino acids are of intrinsic interest pertaining to characteristic aggregation patterns. Carboxylic acids are simple organic molecules that are believed to have existed in the prebiotic earth and some of them are key intermediates in the biosynthesis of organic acids. Precise crystallographic data on complexes of amino acids with carboxylic acids are expected to provide useful insights into chemical evolution and self-assembly, processes that might have led to the emergence of primitive multi-molecular systems.

A thorough literature survey revealed that only a few amino acid–trifluoroacetic acid complexes have been reported so far. This prompted the author to attempt the crystallization of several amino acid–trifluoroacetic acid complexes and the author could successfully crystallize two more amino acid complexes with trifluoroacetic acid. A search in the Cambridge Structural Database (April 2004) revealed only a few amino acid–benzoic acid complexes. This further motivated the author to attempt crystallization of several amino acid–benzoic acid complexes, owing to the importance of benzoic acid in the biological systems. The author was successful in getting only one amino acid–benzoic acid complex.

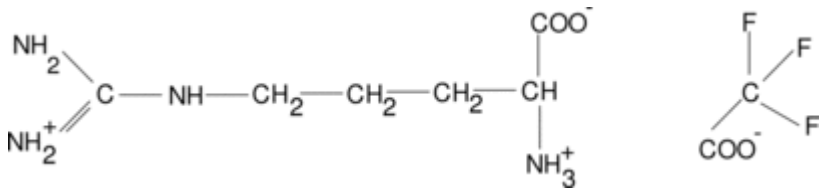
In **Part II (Chapters 6 and 7)** of this thesis, the X-ray crystal structures of a few amino acid-carboxylic acid complexes are reported. The crystal data along with

the R-factors of the crystal structures of the compounds are given in Table 2. The crystal structures reported are :



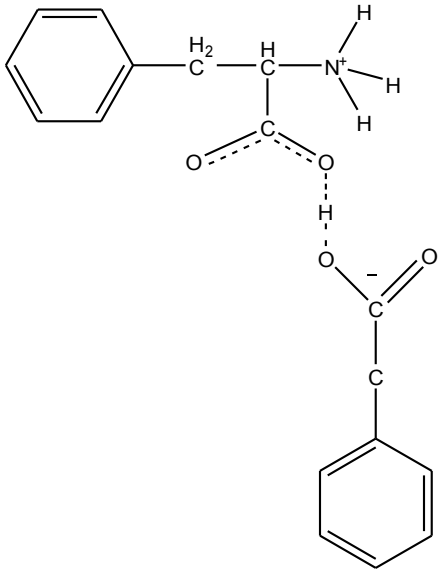
15. DL-valinium trifluoroacetate

$[C_5H_{12}NO_2^+.C_2F_3O_2^-]$ **(Compound 15)**



16. L-arginine trifluoroacetate.

$[C_6H_{15}N_4O_2^+.C_2F_3O_2^-]$ **(Compound 16)**



17. L-phenylalanine benzoic acid.

$[C_9H_{11}NO_2.C_7H_6O_2]$ **(Compound 17)**

Chapter 6 describes the structural details of compounds 15 and 16. In 15, DL-valine exists in the cationic form with a protonated amino group and an uncharged carboxylic acid group. In 16, the amino acid exists as a zwitterionic argininium cation, with positively charged amino and guanidinium groups and a negatively charged carboxylate group. The trifluoroacetate anion adopts the most favoured staggered conformation with typical bond lengths and bond angles in compound 16. The head-to-tail hydrogen bond is present in compound 15 and 16, a common feature observed in the case of amino acid-carboxylic acid complexes.

Chapter 7 describes the structural features of L-Phenylalanine benzoic acid. The amino acid molecule exists as a zwitterion, an uncommon ionization state in the crystal structures of amino - carboxylic acid complexes and the benzoic acid molecule exists in the unionized state. The phenylalanine and benzoic acid molecules form hydrogen-bonded double layers linked together by N—H...O and O—H...O hydrogen bonds and extend along [010]. The N—H...O hydrogen bond includes two characteristic head-to-tail types, one between the translationally-related and the other between the screw-related phenylalanine molecules.

Based on the above investigations, the following papers have been published in refereed journals :

LIST OF PUBLICATIONS

1. J. Suresh, V. P. Alex Raja, R. V. Krishnakumar, S. Natarajan : S. Perumal and A. Mostad : 2,6-Bis(2-methylphenyl)-1-nitroso-3,5-diphenylpiperidin-4-one, Acta Cryst. (2005). E61, o2458–o2460.

2. J. Suresh, V. P. Alex Raja, S. Perumal and S. Natarajan : 2,6-Bis(4-methylphenyl) – 1 – nitroso -3,5-diphenyl-2,3,5,6 - tetrahydro pyridine -4(1H)-one, Acta Cryst. (2006). E 62, o3307–o3309.

3. J. Suresh, V. P. Alex Raja, R. V. Krishnakumar, S. Natarajan, S. Perumal and A. Mostad : 2,6-Bis(2-methoxyphenyl)-1-nitroso-3,5-diphenylpiperidin-4-one, Acta Cryst. (2005). E 61,o3050–o3052.

4. J. Suresh, V. P. Alex Raja, S. Natarajan, S. Perumal, A. Mostad and R. V. Krishnakumar : 2,6-Bis(2-chlorophenyl)-1-nitroso-3,5- diphenylpiperidin-4-one, Acta Cryst. (2005). E 61, o3391–o3393.

5. J. Suresh, V. P. Alex Raja, R. V. Krishnakumar, S. Perumal, K. Ravikumar and S. Natarajan : Crystal Structure of 2,6-Bis(4-methylphenyl)-1-nitroso-3-

phenyltetrahydro-4(1*H*)-piperidin-4-one ANALYTICAL SCIENCES 2006, VOL. 22, x223.

6. J. Suresh, R. Suresh Kumar, S. Perumal, A. Mostad and S.Natarajan : Ethyl 4-hydroxy-2, 6-diphenyl-5-(phenylsulfanyl) pyridine-3-carboxylate and ethyl 2,6-bis(4-fluorophenyl)-4-hydroxy-5- (4-methylphenylsulfanyl) pyridine-3-carboxylate: supramolecular aggregation through C—H…O,C—H…F and C—H…π interactions, Acta Cryst. (2007). C 63, o141–o144.

7. J. Suresh, R. Suresh Kumar, S. Perumal and S. Natarajan : Ethyl 2, 6-bis(4-chlorophenyl)-4-hydroxy - 5 - phenyl-1,2,5,6-tetrahydro pyridine-3-carboxylate: supramolecular aggregation through N—H…Cl,C—H…Cl, C—H…S andC—H…π interactions, Acta Cryst. (2007). E 63, o777–o779.

8. J. Suresh, R. Suresh Kumar, S. Perumal and S. Natarajan : (2RS,5SR,6SR)-Ethyl 2,6-bis(4-fluorophenyl)-4-hydroxy-5-phenylsulfanyl-1,2,5,6-tetrahydropyridine-3-carboxylate, Acta Cryst. (2007). E 63, o1377–o1379.

9. J. Suresh, R. Suresh Kumar, S. Perumal and S. Natarajan : (2RS,5RS,6RS)-Ethyl4-hydroxy-2,6-di- p-tolyl-5- p-tolylsulfanyl-1,2,5,6-tetrahydropyridine-3-carboxylate, Acta Cryst. (2007). E63, o1375–o1376.

10. J. Suresh, R. Suresh Kumar, S. Perumal and S. Natarajan : (2SR, 5SR,6SR)-Ethyl5-[(4-chlorophenyl)sulfanyl]-2,6-bis(4-fluorophenyl) -4-hydroxy-1,2,5,6-tetrahydropyridine-3-carboxylate, Acta Cryst. (2007). E 63, o2140–o2141.

11. J. Suresh, R. Suresh Kumar, S. Perumal and S. Natarajan :(R)-3,5-Bis[(E)-benzylidene]-1-(1-phenylethyl)piperidin-4-one,3,5-bis-[(E)-4-chlorobenzylidene]-1-[(R)-1-phenylethyl]piperidin-4-one and 3,5-bis[(E)-2-chlorobenzylidene]-1-[(R)-1-phenylethyl]piperidin-4-one, Acta Cryst. (2007). C 63,o315–318.

12. J. Suresh and S. Natarajan : DL-Valinium trifluoroacetate, Acta Cryst. (2006). E 62, o3331–o3333.

13. J.Suresh, R. V. Krishnakumar and S. Natarajan: L-Argininium trifluoroacetate, Acta Cryst. (2006). E 62, o3127–o3129.

14. J.Suresh,R. V. Krishnakumar and S. Natarajan : L-phenylalanine –benzoic acid (1/1), Acta Cryst. (2005). E 61, o3625–o3627.

TECHNICAL REPORT OF THE THESIS

The thesis contains the crystallographic studies on two distinct groups of compounds and hence is divided into two parts The first part deals with the crystal structure determination of compounds of piperidine/pyridine. The second part deals with the crystal structures of the complexes of some amino acids with trifluoroacetic acid and benzoic acid. For the elucidation of the structures of these molecules at atomic resolution, single crystal X-ray diffraction techniques were employed.

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J. SURESH

Dr. S. Natarajan

Guide.